--142. (New) The method of claim 141, wherein said nucleic acid sequence is SEQ ID NO: 151.--

--143. (New) The method of claim 141, wherein said nucleic acid sequence is SEQ ID NO: 152.--

REMARKS

Summary of the Invention

The invention features methods for inducing myelination of neural cells by glial cells. The methods involve contacting glial cells with polypeptides comprising the epidermal growth factor-like domains of the GGF/p185erbB2 ligand gene disclosed in the specification.

Summary of the Office Action

Claims 132-140 are rejected under 35 U.S.C. § 112, first and second paragraphs, and are rejected and provisionally rejected under the judicially created doctrine of obviousness-type double patenting. In addition, the disclosure is objected to for various informalities.

Support for the Amendments

The specification has been amended. Where the GGF-II/GGF2HBS5 polypeptide was misidentified in the original specification as SEQ ID NO: 167, the polypeptide is now correctly identified as SEQ ID NO:170. Such amendment is made on page 7, line 16, page 32, lines 28-29, and page 66, lines 27-29, of the specification. Support for the foregoing amendments of the GGF-II polypeptide SEQ ID NO (from 167 to 170) may be found, e.g., on page 33, lines 28-29, of the specification. A replacement drawing is provided for Fig. 45 to correct a typographical error that incorrectly identifies GGF II polypeptide as SEQ ID NO: 167.

Substitute drawings are provided for the purpose of clarity. Several of the drawings have been subdivided: for example, Fig. 31 is now divided into Figs. 31A-31R. Corrections to the descriptions of the drawings are made to reflect these subdivisions. No new matter is introduced by these changes.

Three new SEQ ID Nos., 185-187, have been added to the specification at page 13. The peptides assigned these SEQ ID Nos. were present in the original disclosure, but had not been assigned SEQ ID Nos. SEQ ID Nos. 185-187 also have been added to the Sequence Listing provided herewith.

Claims 132, 136, 137, 139, and 140 have been amended, and new claims 141-143 have been added. Support for the amendment to claim 132 may be found, e.g., at page 11, lines 5 through 9, and at page 65, lines 1 through 8, of the specification.

Claims 136 and 137 previously depended from claim 133 (which depended from

claim 132). Support for language added to claims 136 and 137, in order to convert them into independent claims, may be found, e.g., at page 81, lines 9 through 12 of the specification. Additional language added to claims 136 and 137, which specifies the polypeptide segments encoded by the SEQ ID NO's (for example, in claim 136: "...wherein said epidermal growth factor like domain further comprises the polypeptide encoded by SEQ ID NO: 188, wherein the human C/D'-segment polypeptide encoded by SEQ ID NO: 179..."), is supported by Figure 31 of the specification (which shows the amino acid translations of the nucleic acid sequences encoding the GGF polypeptide segments), and in the description of Figure 31 on page 30, line 30, through page 31 line 8.

Claims 136 and 137 are amended to recite new sequences that consist of linked subsequences, as required under 37 C.F.R. § 1.822 (o). In concert with the amendment to the claims, the Sequence Listing has been amended to contain two new sequences. The two new sequences consist of joined sequences present in the original sequence listing in an order described in the originally filed specification. Hence, no new matter is added. Support for new SEQ ID NO: 188 (as provided in claim 136) comes from its subsequences, SEQ ID NO:177 and SEQ ID NO: 179, found in the original Sequence Listing. Similarly, support for new SEQ ID NO: 189 (claim 137) comes from its subsequences, SEQ ID NO:143, SEQ ID NO: 177, and SEQ ID NO: 180, found in the original Sequence Listing. The orientation of the sequences, as claimed, is shown in Fig. 30, and is described in the specification on page 8, lines 3 through 16. Supporting

language for the amendments to claim 136 may be found within Figures 31G and 31I. Similarly, supporting language for the amendments to claim 137 may be found within Figures 31G, 31I, 31J, and within the amended Sequence Listing.

Claims 139 and 140, which previously were independent claims, now depend from claims 132, 136, 137, or 141. Support for these amendments may be found at page 81, lines 9 through 12.

New claim 141 recites a "method for inducing myelination..." using EGF-like domains selected from SEQ ID NOs: 151, 152, or amino acids 362-411 of SEQ ID NO: 170. Support for claim 141 (and dependent claims 142 and 143) may be found, e.g., at page 80, line 26, through page 81, line 12; at page 11, lines 18-21; at page 66, lines 16-21, and at Fig. 35.

No new matter has been introduced by these amendments.

Informalities

The disclosure is objected to for various informalities. First, the GGF II/GGF2HBS5 polypeptide is misidentified as SEQ ID NO: 167 at page 7, line 16, page 32, lines 28-29, and page 66, lines 27 and 29. Second, an amendment to the title and the abstract was requested. Third, the Brief Description of the Drawings was objected to for lack of descriptions for Figs. 9, 11, and 13-20. Fourth, pages 12-13, 61 (line 27), and 66 contain sequences that require SEQ ID NOs. Lastly, claims 136-137 are not in

compliance with the sequence rules: a sequence that is made up of noncontiguous segments of a larger sequence or from different sequences shall be presented as a separate sequence. The informalities have been corrected by the foregoing amendment. No new matter is introduced by these corrections.

Non-Statutory Double Patenting Rejection

Claims 132-140 are rejected as being unpatentable over claims 1 and 2 of U.S. Patent No. 5,602,096, and are provisionally rejected as being unpatentable over claims 132 and 152-154 of co-pending Application No. 08/472,065, over claims 141-148 of co-pending Application No. 08/471,833, over claims 132-162 of co-pending Application No. 08/735,021, over claims 132, 133, 149, 150, and 152 of co-pending Application No. 08/470,339, and over claims 132-140 of co-pending Application No. 08/736,070, under the judicially created doctrine of obviousness-type double patenting. Applicants note the rejection and provisional rejection, and will file any necessary terminal disclaimers once otherwise allowable subject matter has been determined.

Rejections under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 132-140 under 35 U.S.C. §112, first paragraph, as lacking enablement. The Examiner's rejection involves several issues, each of which will be addressed below.

First, the Examiner states that the specification does not provide sufficient guidance because the "GGF/p185erbB2 ligand gene" recited in the claims is a verbal description that does not sufficiently characterize the physical or chemical structure of the gene.

In response, Applicants have canceled claims 133-135 and 138, have amended claims 132, 136, 137, 139, and 140, and have added new claims 141-143. Independent claims 132, 136, and 137 now recite SEQ ID NOs for the EGF-like domains that are encoded by the GGF/p185erbB2 ligand gene of the claim. These include EGFL 1-6; SEQ ID NOs: 151 and 152; amino acids 54-103 encoded by SEQ ID NO: 150 (bovine GGF2 cDNA clone GGFBPP4); and amino acids 362-411 of SEQ ID 170 (GGF2 polypeptide encoded by human cDNA clone GGF2HBS5).

SEQ ID NOs: 151 and 152 are EGF-like domains encoded by bovine cDNA clones GGFBPP5 and GGFBPP4, respectively (see, e.g., Fig. 35, which shows the alignment between the EGF domain from EGF (SEQ ID NO: 153) and SEQ ID NOs: 151 and 152). The sequences of the C-C/D and C-C/D' EGF-like domain polypeptides set forth in SEQ ID NOs: 151 and 152 are identical between humans and bovines. SEQ ID NO: 152 corresponds to amino acids 54-103 encoded by the GGFBPP4 cDNA clone (SEQ ID NO: 150). Likewise, SEQ ID NO: 151 corresponds to amino acids 362-411 of SEQ ID 170. Hence, the sequences of these EGF-like domains are shared between humans and bovines, and, therefore, the claims encompass EGF-like domains from both species. As a

result of the foregoing amendments, the term "GGF/p185erbB2 ligand gene" is now limited in the claims by the recitation of specific sequences encoded by the gene, and hence, the specification enables use of the polypeptides as now recited.

Second, the Examiner states that "epidermal growth factor-like domain" does not provide sufficient characterization to what is enabled in the specification, because an EGF-like domain is not constant in sequence or length. The addition to claim 132 of SEQ ID Nos. that correspond to specific EGF-like domains that are encoded by the GGF/p185erbB2 ligand gene, as described in the specification, eliminates this insufficiency. Hence, this aspect of the rejection may be withdrawn.

Third, the Examiner states that claims 139 and 140 recite polypeptides with functional limitations in the absence of chemical or structural limitations, and hence, the claims encompass polypeptides not taught in the disclosure. Claims 139 and 140 have been amended to depend from claims 132, 136, 137, or 141, which recite SEQ ID NOs for EGF-like domains encoded by the GGF/p185erbB2 ligand gene, as disclosed in the specification. Such amendment places chemical limitations on the recited polypeptides; therefore, this aspect of the rejection may also be withdrawn.

Fourth, the Examiner states that while the claims encompass induction of myelination by glial cells of the central nervous system (CNS), the specification enables only myelination by Schwann cells, which are glial cells of the peripheral nervous system. The Examiner has invited Applicants to submit a Declaration demonstrating that

the specification teaches how to make and use the disclosed GGFs in a manner consistent with the myelination by CNS glial cells.

Applicants' prediction that the claimed GGF/p185erbB2- encoded proteins stimulate myelination by a range of glial cell types, including the glia of the CNS, is supported by experimental evidence. The Examiner is directed to the attached Declaration of Dr. Mark Marchionni, and to the journal article provided therein by Canoll, P.D., Musacchio, J.M., Hardy, R., Reynolds, R., Marchionni, M.A., and Saltzer, J.L., Cell, 17:229 (1996). As Dr. Marchionni notes, Canoll et al. show that recombinant human GGF2 and recombinant heregulin β1, an alternative-splice product of the GGF2 gene provided by the instant application, are mitogenic for several types of glia of the CNS, namely, pro-oligodendrocytes, oligodendrocytes, and type-2 astrocytes. Since mitogenesis of glial cells is a hallmark of myelinating activity, the specification is enabling for the use of GGFs to stimulate myelination of neural cells by CNS glia, and this aspect of the rejection also may be withdrawn.

As amended, claims 132, 136, 137, 139, and 140 should now be allowable under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 132-138 under 35 U.S.C. §112, second paragraph, as being indefinite. First, the Examiner states that the metes and bounds of

"an EGF-like domain" and a "GGF/p185erbB2 ligand gene" are not sufficiently defined in the disclosure to be definitive for the polypeptides and nucleic acids encompassed by the claims. Next, the Examiner states that the claims do not clearly convey the order in which the sequences of claims 136-137 are linked. Last, the Examiner states that the claims recite polypeptides, and the SEQ ID Nos. recited in the claims are not for polypeptides, but for nucleic acids.

Applicants have addressed the above points by canceling claims 133-135 and 138, by adding new claims 141-143, and by amending claims 132, 136, and 137 in several ways.

First, claim 132 and new claim 141 now recite specific SEQ ID NOs for the EGF-like domains. The recited SEQ ID NOs, which were provided in the original disclosure, clearly define the metes and bounds of an EGF-like domain. The addition of these SEQ ID NOs to claim 132 ensures that the metes and bounds of an EGF-like domain are now clearly defined in the claims. And, as a result of reciting specific SEQ ID NOs, the GGF/p185erbB2 ligand gene is also clearly defined, since the gene is described by the sequences that it encodes.

With respect to the metes and bounds of the GGF/p185erbB2 ligand gene itself, these are disclosed in the specification, wherein the isolation of both genomic and cDNA clones comprising the GGF/p185erbB2 ligand gene is described. See Example 4, which describes the isolation of these genomic and cDNA clones, and describes

GGF/p185erbB2 ligand genomic exons and cDNA coding sequences (see, e.g., pages 61-65; see also Figs. 24 and 26, and 30, which show schematic diagrams of GGF/p185erbB2 ligand gene coding regions).

In response to the second basis for the Examiner's indefiniteness rejection, i.e., the ambiguity of the sequence organization in claims 136 and 137, these claims have been amended to more clearly indicate the intended organization. The sequences within claims 136 and 137 are now presented asseparate, larger sequences, in accordance with 37 C.F.R. § 1.822 (o). In addition, to enhance the clarity of these claims, the subsequences contained within each new sequence are recited, along with a definition of the GGF polypeptide segment encoded by each subsequence, and the linear order in which the subsequences are arranged. See, for example, claim 136, which, as amended, recites, "...wherein said epidermal growth factor like domain further comprises the polypeptide encoded by SEQ ID NO: 188, wherein the human C/D'-segment polypeptide encoded by SEQ ID NO: 179 is immediately C-terminal to the human C-segment polypeptide encoded by SEQ ID NO: 177."

Third, with respect to the recitation of SEQ ID NOs that identify nucleic acid sequences instead of polypeptides, the claim language has been changed from "polypeptide set forth in SEQ ID NO..." to "polypeptide encoded by SEQ ID NO...".

In view of the amendments described above, claims 132, 136, and 137 should now be allowable under 35 U.S.C. § 112, second paragraph.

Summary

Applicants submit that the claims are in condition for allowance and such action is requested.

If there are any charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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